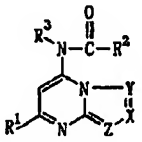
(Abstract)
(Amended)

Object

To put forward an analgesics for inhibiting in particular various pain and a drug composition useful as nitric oxide synthase inhibitor.

Method of Solution

A drug composition containing a condensed ring pyrimidine derivative represented by general formula

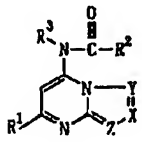


(wherein, R1 denotes an alkyl group or phenyl group, R2 denotes phenyl group, thienyl group, pyridyl group, naphthyl group or phenyl group optionally-containing substituent, R3 denotes hydrogen atom, lower alkyl group or -(CO)R2 (R2 is the same as above), X denotes a nitrogen atom, CH or C-Ph (Ph is phenyl group) and as for Y and Z, when X is a nitrogen atom, Y is CH and and Z is CH, C-CN or $C(CO)NH_2$, and when X is CH or C-Ph, both Y and Z denote nitrogen atom).

Patent Claims

Claim 1

A drug composition containing, as an effective ingredient, a condensed ring pyrimidine derivative represented by general formula



(wherein, R1 denotes an alkyl group or phenyl group, R2 denotes furyl group, thienyl group, pyridyl group, naphthyl group or phenyl group optionally containing 1-3 groups selected from the group comprising lower alkyl group, lower alkoxy group, halogen atom, halogen substituted lower alkyl group, nitro group, phenyl lower alkoxy group, phenoxy group, lower alkyl thio group, lower alkyl sulfinyl group, lower alkyl sulphonyl group, halogen substituted lower alkoxy group, lower alkoxycarbonyl group, cyano group, phenyl group, dilower alkoxy phosphoryl lower alkyl group, N-(trilower alkoxy benzoyl) amino group, lower alkanoyloxy group and hydroxyl group as substituent, R3 denotes hydrogen atom, lower alkyl group or -(CO)R2 (R2 is the same as above), X denotes a nitrogen atom, CH or C-Ph (Ph is phenyl group) and as for Y and Z, when X is a nitrogen atom, Y is CH and and Z is CH, C-CN or $C(CO)NH_2$, and when X is CH or C-Ph, Y and Z respectively denote nitrogen atom).

Claim 2

A drug composition in accordance with Claim 1, wherein in the general formula in accordance with Claim 1, the effective ingredient is selected from the compound wherein R1 is alkyl group and X is CH or C-Ph, and the compound wherein X is nitrogen atom and Z is C-CN or C(CO) NH_2.

Claim 3

A drug composition in accordance with Claim 2, wherein in the general formula in accordance with Claim 1, the effective ingredient is selected from the compound wherein R1 is alkyl group and R3 is hydrogen atom.

Claim 4

A drug composition in accordance with Claim 3, wherein in the general formula in accordance with Claim 1, the effective ingredient is selected from the compound wherein R2 is a naphthyl group or phenyl group containing, as substituent, 1-2 lower alkyl groups, lower alkyl thio groups, halogen substituted lower alkyl groups, halogen atoms, or 3 lower alkoxy groups.

Claim 5

A drug composition in accordance with Claim 4, wherein the effective ingredient is selected from 5-n-butyl-7-(3,4,5-trimethoxy benzoylamino)-1,2,4-triazolo[1,5-a]pyrimidine, 2-n-butyl-8-cyano-4-(2,4-dichloro benzoylamino) imidazo[1,5-a]pyrimidine and 2-n-butyl-8-cyano-4-(3,4,5-trimethoxy benzoyloxy) imidazo[1,5-a]pyrimidine.

Claim 6

A drug composition in accordance with any of Claims 1-5 which is an analgesics.

Claim 7

A drug composition in accordance with any of Claims 1-5 which is a nitric oxide synthase inhibitor.

Claim 8

A drug composition in accordance with any of Claims 1-5 which is an inducible-type nitric oxide synthase inhibitor.

Claim 9

A drug composition in accordance with any of Claims 1-5 which is a prevention and treatment agent of septicaemia.

Claim 10

A drug composition in accordance with any of Claims 1-5 which is an endotoxin shock improvement agent.

Detailed Description of the Invention

(0001)

Technical Sphere of the Invention

This invention relates to the following, namely, a drug composition containing novel condensed ring pyrimidine derivative as the effective ingredient.

(0002)

Technology of the Prior Art

The condensed ring pyrimidine derivatives as the effective ingredient of this invention are novel compounds previously unreported in the literature.

(0003)

Problems to be Overcome by this Invention

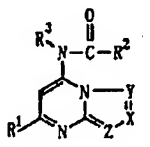
As described later, this invention has the object of putting forward a drug composition comprising the aforesaid novel compounds as the effective ingredient useful as pharmaceutical, for example an analgesics, nitric oxide synthase inhibitor and the like.

(0004)

Means to Overcome these Problems

In accordance with this invention, a drug composition containing the condensed ring pyrimidine derivative represented by following formula (1) as the effective ingredient is put forward.

(0005)



(1)

(0006)

(Wherein, R1 denotes an alkyl group or phenyl group, R2 denotes furyl group, thienyl group, pyridyl group, naphthyl group or phenyl group optionally containing 1-3 groups selected from the group comprising lower alkyl group, lower alkoxy group, halogen atom, halogen substituted lower alkyl group, nitro group, phenyl lower alkoxy group, phenoxy group, lower alkyl thio group, lower alkyl sulfinyl group, lower alkyl sulphonyl group, halogen substituted lower alkoxy group, lower alkoxycarbonyl group, cyano group, phenyl group, dilower alkoxy phosphoryl

lower alkyl group, N-(trilower alkoxy benzoyl) amino group, lower alkanoyloxy group and hydroxyl group as substituent, R3 denotes hydrogen atom, lower alkyl group or -(CO)R2 (R2 is the same as above), X denotes a nitrogen atom, CH or C-Ph (Ph is phenyl group) and as for Y and Z, when X is a nitrogen atom, Y is CH and and Z is CH, C-CN or $C(CO)NH_2$, and when X is CH or C-Ph, Y and Z respectively denote nitrogen atom.)

The condensed ring pyrimidine derivative represented by the aforesaid general formula (1) is useful as pharmaceutical effective ingredient. In particular, aforesaid derivative is useful as an analgesics (postoperative pain, migraine headache, gout, chronic pain, neurogenic pain, cancerous pain or the like), anti-inflammatory drug, antibacterial drug, hypoglycemic drug, lipid lowering agent, blood pressure lowering agent, carcinostatic and the like, and among these it is preferably used as an analgesics, and this has the characteristic that it is almost free from side effects which is common in a prior art analgesics.

(0007)

Moreover, the aforesaid derivative has an action to inhibit nducible-type nitric oxide synthase selectively, and it is useful for prevention and treatment of for example septicaemia, endotoxin shock, chronic rheumatism and the like as the said synthase inhibitor. In particularly, such nitric oxide synthase inhibitor has the advantage that it is almost free from side effects which is common in a prior art nitric oxide synthase inhibitor.

(0008)

The Form of Carrying Out The Invention

The following groups can be exemplified respectively as each group defined in the aforesaid general formula (1) which represents derivative of this invention. Wherein, the term "lower" used in such groups denote the carbon number 1-6.

(0009)

As lower alkyl group, straight chain or branched chain state lower alkyl group such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, pentyl, hexyl group and the like can be exemplified. Moreover, as far as alkyl group is concerned, in addition to the aforesaid lower alkyl group, heptyl, octyl, nonyl, decyl group can be exemplified.

(0010)

As lower alkoxy group, methoxy, ethoxy, propoxy, isopropoxy, butoxy, pentyloxy, hexyloxy groups can be exemplified.

(0011)

Fluorine atom, chlorine atom, bromine atom and iodine atom are included in halogen atom.

(0012)
As halogen substituted lower alkyl group, trifluoromethyl, pentafluoro ethyl, heptafluoro propyl, nonafluoro butyl, undeca fluoro pentyl, trideca fluoro hexyl group can be exemplified.

(0013)
In furyl group, 2-furyl and 3-furyl groups are included.

(0014)
In thienyl group, 2-thienyl and 3-thienyl groups are included.

(0015)
In pyridyl group, 2-pyridyl, 3-pyridyl and 4-pyridyl groups are included.

(0016)
In naphthyl group, 1-naphthyl and 2-naphthyl groups are included.

(0017)
As phenyl lower alkoxy group, benzyloxy, 2-phenyl ethoxy, 3-phenyl propoxy, 4-phenyl butoxy, 5-phenyl pentyloxy, 6-phenylhexyl oxy group can be exemplified.

(0018)
As lower alkyl thio group, methylthio, ethylthio, propylthio, butylthio, pentyl thio, hexyl thio group can be exemplified.

(0019)
As lower alkyl sulfinyl group, methylsulfinyl, ethyl sulphinyl, propylsulphinyl, butyl sulphinyl, pentyl sulphinyl, hexyl sulfinyl group can be exemplified.

(0020)
As lower alkyl sulphonyl group, methylsulfonyl, ethylsulfonyl, propyl sulfonyl, butylsulfonyl, pentyl sulfonyl, hexyl sulphonyl group can be exemplified.

(0021)
As halogen substituted lower alkoxy group, trifluoromethoxy, pentafluoro ethoxy, heptafluoropropoxy, nonafluoro butoxy, undeca fluoro pentyloxy, trideca fluoro hexyloxy group can be exemplified.

(0022)

As lower alkoxycarbonyl group, methoxycarbonyl, ethoxycarbonyl, propoxy. carbonyl, butoxycarbonyl, pentyl oxycarbonyl, hexyl oxycarbonyl group can be exemplified.

(0023)

As dilower alkoxy phosphoryl lower alkyl group, dimethoxyphosphoryl methyl, diethoxy phosphoryl methyl, dipropoxy phosphoryl methyl, dibutoxy phosphoryl methyl, dipentyloxy phosphoryl methyl, dihexyl oxy phosphoryl methyl, 2-(dimethoxyphosphoryl) ethyl, 2-(diethoxy phosphoryl) ethyl, 3-(diethoxy phosphoryl) propyl, 4-(diethoxy phosphoryl) butyl, 5-(diethoxy phosphoryl) pentyl, 6-(diethoxy phosphoryl) hexyl group can be exemplified.

(0024)

As N-(tri lower alkoxy benzoyl) amino group, n-(3,4,5-trimethoxy benzoyl) amino, N-(3,4,5-tri ethoxy benzoyl) amino, N-(3,4,5-tri propoxy benzoyl) amino, N-(2,3,4-trimethoxy benzoyl) amino, N-(2,4,5-trimethoxy benzoyl) amino group can be exemplified.

(0025)

As phenyl group optionally containing 1-3 groups, as substituent, selected from the group comprising lower alkyl group, lower alkoxy group, halogen atom, halogen substituted lower alkyl group, nitro group, phenyl lower alkoxy group, phenoxy group, lower alkyl thio group, lower alkyl sulfinyl group, lower alkyl sulphonyl group, halogen substituted lower alkoxy group, lower alkoxycarbonyl group, cyano group, phenyl group, dilower alkoxy phosphoryl lower alkyl group, N-(trilower alkoxy benzoyl) amino group, lower alkanoyloxy group and hydroxyl group, the following each substituted phenyl group can be exemplified other than unsubstituted phenyl group.

(0026)

2-methylphenyl, 3-methylphenyl, 4-methylphenyl, 4-ethylphenyl, 4-propyl phenyl, 4-butylphenyl, 4-t-butylphenyl, 4-pentylphenyl, 4-hexyl phenyl, 2,3-dimethyl phenyl, 2,4-dimethyl phenyl, 3,4-dimethyl phenyl, 3,5-dimethyl phenyl, 3,4,5-trimethylphenyl, 2-methoxyphenyl, 3-methoxyphenyl, 4-methoxyphenyl, 4-ethoxyphenyl, 4-propoxy phenyl, 4-butoxy phenyl, 4-pentyloxyphenyl, 4-hexyloxyphenyl, 2,3-dimethoxyphenyl, 2,4-dimethoxyphenyl, 2,5-dimethoxyphenyl, 2,6-dimethoxyphenyl, 3,4-dimethoxyphenyl, 3,5-dimethoxyphenyl, 2,3,4-trimethoxyphenyl, 2,3,5-trimethoxyphenyl, 2,3,6-trimethoxyphenyl, 2,4,5-trimethoxyphenyl, 2,4,6-trimethoxyphenyl, 3,4,5-trimethoxyphenyl, 3,4,5-tri ethoxyphenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2-chlorophenyl, 3-chlorophenyl, 4-chlorophenyl, 2-bromo phenyl. 3-bromo phenyl, 4-bromo phenyl, 4-iodophenyl, 2,3-dichlorophenyl, 2,4-dichlorophenyl, 2,5-

dichlorophenyl, 2,4,6-trichlorophenyl, 2,4-dichloro-5-fluorophenyl, 2-trifluoromethylphenyl, 3-trifluoromethylphenyl, 4-trifluoromethylphenyl, 4-pentafluoro ethylphenyl, 4-heptafluoro propyl phenyl, 4-nonafluoro butylphenyl, 4-undeca fluoro pentylphenyl, 4-trideca fluoro hexyl phenyl, 2,3-bis (trifluoromethyl) phenyl, 2,4-bis (trifluoromethyl) phenyl, 3,4-bis (trifluoromethyl) phenyl, 3,5-bis (trifluoromethyl) phenyl, 3,4,5-tris (trifluoromethyl) phenyl, 2-nitrophenyl, 3-nitrophenyl, 4-nitrophenyl, 2-benzyloxyphenyl, 3-benzyloxyphenyl, 4-benzyloxyphenyl, 4-(2-phenyl ethoxy) phenyl, 4-(3-phenyl propoxy) phenyl, 4-(4-phenyl butoxy) phenyl, 4-(5-phenyl pentyloxy) phenyl, 4-(6-phenylhexyl oxy) phenyl. 2,4-dibenzyl oxy phenyl, 3,5-dibenzyl oxy phenyl, 4-benzyloxy-3,5-dimethoxyphenyl, 2-phenoxyphenyl, 3-phenoxyphenyl, 4-phenoxyphenyl, 2-methylthio phenyl, 3-methylthio phenyl, 4-methylthio phenyl, 4-ethylthio phenyl, 4-propylthio phenyl, 4-butylthio phenyl, 4-pentyl thiophenyl, 4-hexyl thiophenyl, 2,4-dimethyl thiophenyl, 3,4-dimethyl thiophenyl, 3,5-dimethyl thiophenyl, 2-methylsulfinyl phenyl, 3-methylsulfinyl phenyl, 4-methylsulfinyl phenyl, 4-ethyl sulphinyl phenyl, 4-propylsulphinyl phenyl, 4-butyl sulphinyl phenyl, 4-pentyl sulphinyl phenyl, 4-hexyl sulphinyl phenyl, 2-methylsulfonyl phenyl, 3-methylsulfonyl phenyl, 4-methylsulfonyl phenyl, 4-ethylsulfonyl phenyl, 4-propyl sulfonyl phenyl, 4-butylsulfonyl phenyl, 4-pentyl sulfonyl phenyl, 4-hexyl sulfonyl phenyl, 2-trifluoromethoxyphenyl, 3-trifluoromethoxyphenyl, 4-trifluoromethoxyphenyl, 4-pentafluoro ethoxyphenyl, 4-heptafluoropropoxy phenyl, 4-nonafluoro butoxy phenyl, 4-undeca fluoro pentyloxyphenyl, 4-trideca fluoro hexyloxyphenyl, 2-carbomethoxyphenyl, 3-carbomethoxyphenyl, 4-carbomethoxyphenyl. 4-ethoxycarbonyl phenyl, 4-propoxy carbonyl phenyl, 4-butoxycarbonyl phenyl, 4-pentyl oxycarbonyl phenyl, 4-hexyl oxycarbonyl phenyl, 2-cyanophenyl, 3-cyanophenyl, 4-cyanophenyl, (1,1'-biphenyl)-4-yl, (1,1'-biphenyl)-3-yl (1,1'-biphenyl)-2-yl, 2-(diethoxy phosphoryl methyl) phenyl, 3-(diethoxy phosphoryl methyl) phenyl, 4-(diethoxy phosphoryl methyl) phenyl, 4-(dimethoxyphosphoryl methyl) phenyl, 4-(dipropoxy phosphoryl methyl) phenyl, 4-(dibutoxy phosphoryl methyl) phenyl, 4-(dipentyloxy phosphoryl methyl) phenyl, 4-(dihexyl oxy phosphoryl methyl) phenyl, 4-(2-(dimethoxyphosphoryl) ethyl) phenyl, 4-(2-(diethoxy phosphoryl) ethyl) phenyl, 4-(N-[3,4,5-trimethoxy benzoyl] amino) phenyl, 3-(N-[3,4,5-trimethoxy benzoyl] amino) phenyl, 2-(N-[3,4,5-trimethoxy benzoyl] amino) phenyl, 4-(N-[3,4,5-tri ethoxy benzoyl] amino) phenyl, 4-(N-[3,4,5-tri propoxy benzoyl] amino) phenyl, 4-(N-[2,3,4-trimethoxy benzoyl] amino) phenyl, 4-(N-[2,4,6-trimethoxy benzoyl] amino) phenyl, 2-acetoxyphenyl, 3-acetoxyphenyl, 4-acetoxyphenyl, 4-propionyloxy phenyl, 4-butyryl oxy phenyl, 4-valeryl oxy phenyl, 4-pivaloyloxy phenyl, 4-hexanoyloxy phenyl, 4-heptanoyloxy phenyl, 2,3-diacetoxy phenyl, 2,4-diacetoxy phenyl, 3,4-diacetoxy phenyl, 3,5-diacetoxy phenyl, 3,4,5-triacetoxy phenyl, 4-acetoxy-3,5-dimethoxyphenyl, 2-hydroxyphenyl, 3-hydroxyphenyl, 4-hydroxyphenyl, 2,3-dihydroxyphenyl, 2,4-dihydroxyphenyl, 3,4-dihydroxyphenyl, 3,5-dihydroxyphenyl, 3,4,5-trihydroxyphenyl.

(0027)

Preferred derivative represented by the aforesaid general formula (1) of this invention as an active ingredient of pharmaceutical is selected from the compound wherein R1 is alkyl group and X is CH or C-Ph, and compound wherein X is nitrogen atom and Z is C-CN or $C(CO)NH_2$ in the said general formula (1), and among these, the one in which R1 is alkyl group and R3 is hydrogen atom is more preferably. Moreover, among these preferable condensed ring pyrimidine derivatives, it is further preferred the one wherein R2 is naphthyl group or phenyl group containing, as substituent, 1-2 lower alkyl thio groups, halogen substituted lower alkyl groups, halogen atoms or 3 lower alkoxy groups.

(0028)

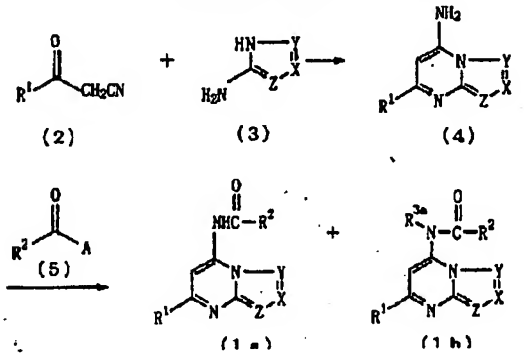
As the most preferred embodiment example of effective ingredient in the drug composition of this invention, 5-n-butyl-7-(3,4,5-trimethoxy benzoylamino)-1,2,4-triazolo[1,5-a]pyrimidine, 2-n-butyl-8-cyano-4-(2,4-dichloro benzoylamino) imidazo[1,5-a]pyrimidine and 2-n-butyl-8-cyano-4-(3,4,5-trimethoxy benzoyloxy) imidazo[1,5-a]pyrimidine can be examplified.

(0029)

The condensed ring pyrimidine derivatives comprising the effective ingredient of this invention can be produced using various processes. The example will be explained in detail by reference to Reaction Steps as follows.

(0030)

Reaction Step-1



(0031)

(Wherein, R1, R2, X, Y and Z are the same as above, R3a is a group -(CO)R2 (R2 is the same as above), and A denotes a halogen atom.)

In the aforesaid reaction step formula-1, the condensation reaction of nitrile derivative (2) and compound (3) is carried out in inert solvent such as for example benzene, toluene, xylene, acetic

acid, ethanol and the like under the condition of the temperature in a range of room temperature to reflux temperature over a period of 3-50 hours approx. Moreover, it is general that used rate of both compounds is approximately equimolar quantity.

(0032)

Thereafter, compound (4) obtained by the aforesaid reaction can be converted to the compound of this invention (1a) by reacting with acid halide (5). Moreover, during this procedure, there is the case to obtain the compound (1b) as the coproduct. This reaction can be carried out in the presence of deoxidizer in a suitable solvent. Wherein as solvent, for example aromatic to aliphatic hydrocarbons such as benzene, toluene, xylene, light petroleum and the like, chain-form to cyclic ethers such as diethyl ether, dimethoxyethane, tetrahydrofuran (THF), 1,4,-dioxane and the like, ketones such as acetone, ethyl methyl ketone, acetophenone and the like, halogenated hydrocarbon such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane and the like can be exemplified. Moreover as deoxidizer, for example tertiary amines such as triethylamine, N,N-diethylaniline, N-methylmorpholine, pyridine, 4-dimethylaminopyridine and the like, alkali metal hydride such as sodium hydride, potassium hydride and the like can be preferably exemplified.

(0033)

The quantity used of acid halide (5) and deoxidizer with respect to compound (4) in the aforesaid reaction is not restricted in particular, but it is usually suitable that the acid halide is used approximately equimolecular amount and the deoxidizer is used equimolecular amount-excess molar amount, and reaction is completed in about 0.5-20 hours under the condition of the range of room temperature to reflux temperature. Moreover, generally, if the quantity used of acid halide is increased, there is a tendency to increase the yield of compound (1b).

(0034)

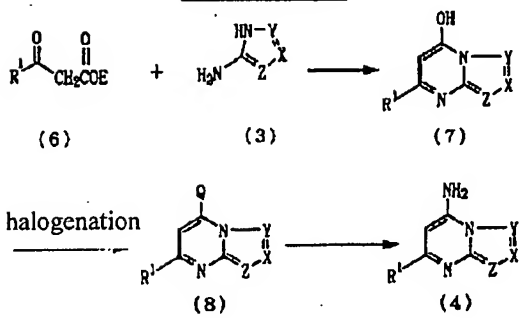
Moreover, it is possible to obtain the compound (1b) by carrying out the reaction with acid halide (5) once again with respect to compound (1a) in the same way as above .

(0035)

Wherein, intermediate compound (4) in the said Reaction Step-1 can be produced by process shown in for example following Reaction Step-2.

(0036)

Reaction Step-2



(6) (3) (7) (8) (4)

(0037)

(Wherein, R1, X, Y and Z are the same as above, E denotes a lower alkyl group and Q denotes a halogen atom respectively.)

The condensation reaction of compound (6) and compound (3) in the aforesaid Reaction Step-2 is carried out in suitable inert solvent under the temperature condition in a range of room temperature-boiling point of solvent. As inert solvent used therein, for example acetic acid, ethanol, benzene, toluene, xylene, THF can be exemplified. In general, used rate of compound (6) and compound (3) is suitably made almost equimolar amount, and reaction is completed to require the time over a period of about 2-5 hours.

(0038)

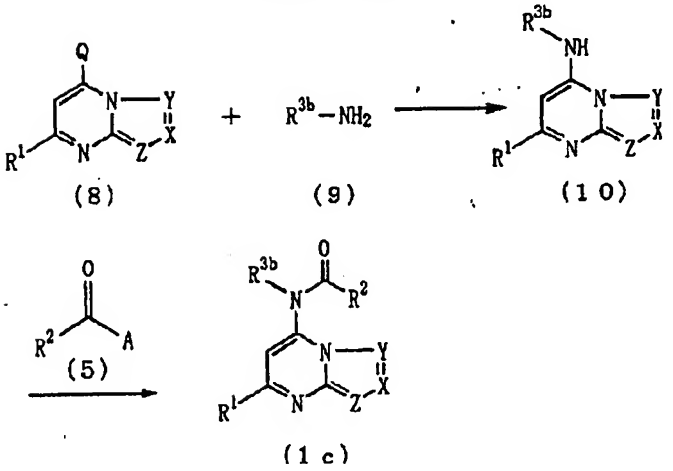
Halogenation of compound (7) obtained in the aforesaid can be carried out using suitable halogenating agent, for example phosphorus oxychloride, phosphorous oxybromide and the like. Because the aforesaid halogenating agent has a role of the solvent, too, solvent is not required to use in particularly in the said reaction, but other inert solvent such as benzene, toluene, xylene and the like may be used. Moreover, in accordance with requirements, deoxidizer such as N,N-dimethylaniline, N,N-diethylaniline, triethylamine and the like can be added in 1-10 times molar quantity. The reaction is carried out under the temperature condition of room temperature-150°C approx over a period of about 0.5-12 hours.

(0039)

Halide (8) obtained by the aforesaid reaction can be converted to compound (4) by treating with ammonia water. The solvent is not reqiored in particular for this treatment, and usually can be carried out by heating compound (8) together with excess ammonia water for 1-12 hours approx at around 100-150°C.

(0040)

Reaction Step-3



(8) (9) (10)

(1c)

(0041)

(Wherein, R1, R2, A, Q, X, Y and Z are the same as above. R3b denotes a lower alkyl group.)

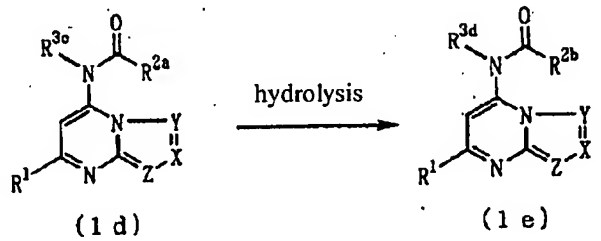
The effective ingredient compound of this invention (1c) can be produced using process shown in the said Reaction Step-3. In other words, firstly the compound (8) and amine (9) are treated for about 1-6 hours under the temperature condition of about reflux temperature in the presence of deoxidizer such as sodium bicarbonate, sodium carbonate, potassium carbonate and the like in an inert solvent such as methanol, ethanol and the like, and by reacting the thereby obtained compound (10) with acid halide (5), it can be made into compound (1c).

(0042)

The reaction of acid halide (5) and the aforesaid compound (10) can be carried out in accordance with process shown in former Reaction Step-1.

(0043)

Reaction Step-4



(1d) (1e)

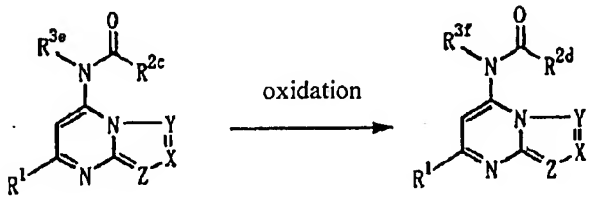
(0044)

(Wherein, R1, X, Y and Z are the same as above. R2a denotes a phenyl group containing lower alkanoyloxy group as substituent and also optionally containing 1-2 groups selected from the lower alkyl group, lower alkoxy group, halogen atom, halogen substituted lower alkyl group, nitro group, phenyl lower alkoxy group, phenoxy group, halogen substituted lower alkoxy group, cyano group, phenyl group and lower alkanoyloxy group. R3c denotes a hydrogen atom, lower alkyl group or group-(CO)-R2a (R2a is the same as above), R2b denotes the one wherein a part corresponding to lower alkanoyloxy group in substituted phenyl group defined by R2a becomes hydroxyl group. R3d denotes a hydrogen atom, lower alkyl group or group-(CO)-R2b (R2b is the same as above).)

The effective ingredient compound of this invention (1d) can be converted to the effective ingredient compound of this invention (1e) by hydrolysing. The said hydrolysis reaction can be carried out by treating with sodium hydroxide aqueous solution, potassium hydroxide aqueous solution in an inert solvent such as methanol, ethanol and the like. Generally, the reaction is completed in 10 mins-3 hours under temperature condition of 0°C-room temperature.

(0045)

Reaction Step-5



(1 f) (1 g)

(0046)

(Wherein, R1, X, Y and Z are the same as above. R2c denotes a phenyl group containing lower alkyl thio group as substituent and also optionally containing 1-2 groups selected from the lower alkyl group, lower alkoxy group, halogen atom, halogen substituted lower alkyl group, nitro group, phenyl lower alkoxy group, phenoxy group, halogen substituted lower alkoxy group, cyano group, phenyl group and lower alkyl thio group. R3e denotes a hydrogen atom, lower alkyl group or group-(CO)-R2c (R2c is the same as above), R2d denotes the one wherein a part corresponding to lower alkyl thio group in substituted phenyl group defined by R2c becomes lower alkyl sulfinyl group or lower alkyl sulphonyl group and R3f denotes a hydrogen atom, lower alkyl group or group-(CO)-R2d (R2d is the same as above).)

Oxidation reaction of compound (1f) is carried out using hydrogen peroxide water, m-chloroperbenzoic acid, sodium periodate and the like as oxidant in inert solvent such as acetic acid, dichloromethane, carbon tetrachloride and the like.

(0047)

Wherein, when the aforesaid oxidation reaction is confined at lower alkyl sulfinyl group, the quantity of the said oxidant used is made 1-small excess of equivalent amount and reaction may be carried out for 15 mins-2 hours at temperature of 0°C-room temperature approx.

(0048)

On the other hand, when the aforesaid oxidation reaction is proceeded to lower alkyl sulphonyl group, the quantity of the said oxidant used is made 2-excess equivalent, and moreover reaction may be carried out with the addition of catalyst such as sodium tungstate and the like in accordance with requirements, for 15 mins-2 hours at room temperature to reflux temperature approx. Moreover, it is also possible to produce the said sulfonyl compound by oxidising the aforesaid sulfinyl compound once again. The reaction conditions in that case may be any of 2 of the aforesaid conditions.

(0049)

The effective ingredient compound of this invention can be made into the pharmacologically acceptable acid addition salt by causing to undergo an addition reaction with suitable acidic compound according to normal method, and the effective ingredient of the drug composition of this invention includes such acid addition salts. The said acid addition salts have the pharmacological activity same as the free-formed compound, and in the same way, it can be used as an active ingredient of pharmaceutical.

(0050)

As the acidic compound which can form the aforesaid acid addition salt, for example inorganic acid such as hydrochloric acid, sulphuric acid, phosphoric acid, hydrobromic acid or the like and organic acid such as maleic acid, fumaric acid, malic acid, tartaric acid, citric acid, methanesulfonic acid, benzenesulfonic acid or the like can be examplified.

(0051)

Moreover, among the compounds of this invention, the compound wherein R3 is hydrogen atom can be made into other copper salts such as alkali metal salt, for example sodium salt, potassium salt and the like and alkaline earth metal salt, for example calcium salt, magnesium salt and the like in accordance with normal methods, and such salts are included in the range of the effective

ingredient of this invention, and can be used as an active ingredient of pharmaceutical in the same way.

(0052)
The target compound obtained using the aforesaid each step can be readily isolated and purified by ordinary separation means. As this separation means, various conventional processes, for example solvent extraction method, recrystallization method, column chromatography, ion exchange chromatography and the like can be exemplified.

(0053)
The drug composition of this invention is made into a general drug preparation using the said effective ingredient compound together with suitable non-toxic carrier, and used. As the aforesaid carrier used for drug preparation, corresponding to conditions of use of preparation, usually used diluent or excipient such as filler, expander, binding agent, humectant, disintegrating agent, surface active agent, lubricant can be given as example and these are suitably selected and used corresponding to administration unit form of preparation to be obtained.

(0054)
As administration unit form of the aforesaid drug composition (drug preparation), various forms can be selected corresponding to therapy objective, and, as representative examples thereof, tablet, pill, powder, liquid agent, suspension, emulsion, granule, encapsulated formulation, suppository, injection (liquid agent, suspension or the like), ointment and the like may be proposed.

(0055)
When forming into tablet, as the aforesaid preparation carrier, for example excipient such as lactose, refined sugar, sodium chloride, glucose, urea, starch, calcium carbonate, kaolin, crystalline cellulose, silica, potassium phosphate and the like, binding agent such as water, ethanol, propanol, single syrup, glucose liquid, starch liquid, gelatin solution, carboxymethylcellulose, hydroxypropylcellulose, methyl cellulose, polyvinylpyrrolidone and the like, disintegrating agent such as carboxymethylcellulose sodium, carboxymethylcellulose calcium, low degree of substitution hydroxypropylcellulose, dry starch, sodium alginate, agar powder, laminaran powder, sodium bicarbonate, calcium carbonate and the like, surfactant such as polyoxyethylene sorbitan fatty acid esters, sodium lauryl sulfate, stearic acid monoglyceride and the like, inhibitor of disintegration such as refined sugar, stearin, cacao butter, hydrogenated oil or the like, adsorption enhancer such as quaternary ammonium salt group, sodium lauryl sulfate and the like, moisture retaining agent such as glycerol, starch and the like, adsorbent such

as starch, lactose, kaolin, bentonite, colloidal silica or the like, lubricant such as purified talc, stearate, boric acid powder, polyethyleneglycol and the like can be used.

(0056)

Further the tablet can be made into the tablet coated with ordinary agent coating in accordance with requirements, for example sugar coated tablet, gelatin encapsulation tablet, enteric coated tablet, film coating tablet or double tablet, multilayer tablet.

(0057)

When formed into the form of a pill, excipient such as for example carrier such as glucose, lactose, starch, cacao butter, hardened vegetable oil, kaolin, talc and the like, binding agent such as powdered gum arabic, tragacanth powder, gelatin, ethanol and the like, disintegrating agent such as laminaran, agar and the like can be used as preparation carrier.

(0058)

When formed into a form of suppository, as preparation carrier, for example polyethyleneglycol, cacao butter, higher alcohol, esters of higher alcohol, gelatin, semi-synthetic glyceride and the like can be used.

(0059)

Encapsulated formulation is usually prepared according to normal method, by mixing effective ingredient compound of this invention with the various preparation carrier exemplified above and packing into hard gelatin capsule, soft capsule and the like.

(0060)

When the drug preparation of this invention is prepared as injection agent such as liquid agent, emulsion, suspension and so on, such materials are sterilized and preferably made isotonic with blood, and when formed into such forms, as a diluent, for example, water, ethanol, macrogol, propylene glycol, ethoxylation isostearyl alcohol, polyoxyisosteary alcohol, polyoxyethylene sorbitan fatty acid ester species as can be used. Moreover, in this case, sufficient sodium chloride, dextrose or glycerol to form an isotonic solution may be contained in agent of this invention, and moreover ordinary solubilizer, buffer agent, analgesic or the like may be added.

(0061)

Furthermore, in the drug preparation of this invention, colorant, preservative, odorant, flavor agent, sweetener and so on and other pharmaceutical can be contained in accordance with requirements.

(0062)

When formed into a form of ointment such as paste, cream, gel and the like, for example white petrolatum, paraffin, glycerol, cellulose derivative, polyethyleneglycol, silicone, bentonite and the like can be used as diluent.

(0063)

The amount of effective ingredient compound represented by general formula (1) to be contained in he drug preparation of this invention is suitably selected from a wide range without restriction in particular, but usually one containing an amount of about 1-70 wt.% approximately in the drug preparation is satisfactory.

(0064)

Administration method of the drug preparation of this invention is not limited in particular, and it is determined corresponding to various formulations, age of patient, the distinction of sex, other conditions, degree of disease or the like. For example, tablet, pill, liquid agent, suspension, emulsion, granule and encapsulated formulation are administered orally, and injection is used alone or mixed with ordinary adjuvant fluid such as dextrose, amino acid or the like, and administered intravenously, and further it is administered alone intramuscularly, intracutaneously, subcutaneously or intraperitoneally in accordance with requirements, and, the suppository is administered rectally.

(0065)

The dose of the aforesaid drug preparation is suitably selected by using the method of use thereof, age of patient, the distinction of sex, other conditions, degree of disease or the like, but usually the amount of the effective ingredient compounds is about 0.5-20 mg, preferably 1-10 mg per 1 kg bodyweight per day, and said preparation can be administered by being divided 1-4 times per day.

(0066)

Examples

Hereinafter, in order to describe this invention in further detail, production examples of raw material compound for production of the compound which is the effective ingredient of this invention may be proposed as Reference Examples, and then production examples of the effective ingredient compounds of this invention may be proposed as Examples. Furthermore, Pharmaceutical Test Examples carried out by using such effective ingredient compounds and Preparation Examples prepared the drug composition of this invention are proposed.

(0067)

Reference Example 1

Production of 4-amino-8-cyano-2-phenylimidazo[1,5-a]pyrimidine

5-amino-4-cyanoimidazole 1.9 g and benzoyl acetonitrile 2.6 g were dissolved in acetic acid 5 ml, and the mixture was stirred at 100°C for 24 hours. The reaction liquor was concentrated under reduced pressure, and chloroform-ethyl acetate was added to the residue, the precipitated crystals were recovered by filtration, washed successively with water and ethyl acetate and recrystallised from ethanol, and the target compound 630 mg (mp.: 314-316°C) was obtained.

(0068)

Reference Examples 2-10

In the same way as in Reference Example 1, following raw material compounds were produced.

(0069)

(2) 4-amino-2-n-butyl-8-cyano imidazo[1,5-a]pyrimidine (mp.: 256-258°C),

(3) 7-amino-5-ethyl-1,2,4-triazolo[1,5-a]pyrimidine (mp.: 194-197°C, recrystallization solvent: ethanol-n-hexane),

(4) 7-amino-5-n-propyl-1,2,4-triazolo[1,5-a]pyrimidine (mp.: 139-142°C, recrystallization solvent: ethanol-n-hexane),

(5) 7-amino-5-n-butyl-1,2,4-triazolo[1,5-a]pyrimidine (mp.: 149-151°C, recrystallization solvent: chloroform-n-hexane),

(6) 7-amino-5-n-pentyl-1,2,4-triazolo[1,5-a]pyrimidine (mp.: 178-181°C, recrystallization solvent: ethanol-n-hexane)

(7) 7-amino-5-n-octyl-1,2,4-triazolo[1,5-a]pyrimidine (mp.: 148-150°C, recrystallization solvent: ethanol-n-hexane),

(8) 4-amino-2-n-butyl-8-carbamoyl imidazo[1,5-a]pyrimidine,

(9) 7-amino-5-n-butyl-2-phenyl-1,2,4-triazolo[1,5-a]pyrimidine (mp.: 211-213°C, recrystallization solvent: ethanol-n-hexane),

(10) 7-amino-5-ethyl-2-phenyl-1,2,4-triazolo[1,5-a]pyrimidine (mp.: 224-226°C, recrystallization solvent: ethanol-n-hexane).

(0070)

Reference Example 11

Production Step (1) of 7-amino-5-n-butyl-1,2,4-triazolo[1,5-a]pyrimidine

3-amino-1,2,4-triazole 34.6 g and 3-oxo heptanoic acid methyl ester 65.0 g of toluene 40 ml solution were heated under reflux at 110°C for three hours. It was cooled, and thereafter, toluene was distilled under reduced pressure, and the residue was recrystallised from ethanol-n-hexane,

and colourless crystals 63.9 g of 5-n-butyl-7-hydroxy-1,2,4-triazolo[1,5-a]pyrimidine was obtained.

(0071)

Step (2)

Oxy basic phosphorus 80 ml was added to 19.2 g crystals obtained in the aforesaid Step (1), and the mixture was heated under reflux for one hour. On completion of the reaction, it was concentrated under reduced pressure, and the residue was discharged into iced water, and the mixture was neutralized with anhydrous sodium acetate, extracted with dichloromethane, and the organic layer was recovered. This was washed with saturated aqueous sodium chloride solution, and thereafter dried with anhydrous sodium sulphate, and concentration was carried out under reduced pressure. The obtained residue was purified by silica gel column chromatography (eluate: ethyl acetate : n-hexane = 1 : 2), and pale red oily substance 14.9 g of 5-n-butyl-7-chloro-1,2,4-triazolo[1,5-a]pyrimidine was obtained.

(0072)

Compound 8.8 g obtained in the aforesaid step and 25 % ammonia water 100 ml were enclosed in stainless sealed tube and it was heated at 120°C for 22 hours. After cooling, the precipitated crystals were recovered by filtration, and after washing with water, recrystallised from methanol-n-hexane, and colourless crystals 3.7 g of target compound were obtained. This was the same compound shown in Reference Example 5 (5).

(0073)

Example 1

Production of 8-cyano-2-phenyl-4-(3,4,5-trimethoxy benzoylamino) imidazo[1,5-a]pyrimidine

Crystals 300 mg obtained in Reference Example 1 was added in pyridine 3.0 ml, and while stirring under ice-cooling, 3,4,5-trimethoxy benzoyl chloride 294 mg was added. This suspension was stirred at 0°C for one hour, and thereafter at room temperature for ten hours. Chloroform was added to the liquid reaction mixture, and the precipitated crystals were recovered by filtration, washed successively with water, ethanol and chloroform, and crystals 100 mg of target compound was obtained. The structure and melting point of the obtained compounds are shown in Table 1.

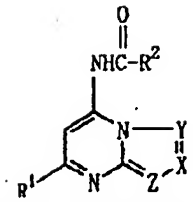
(0074)

Examples 2-13

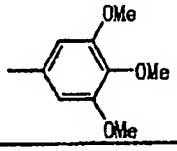
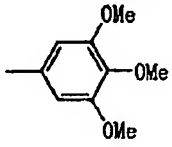
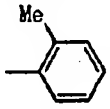
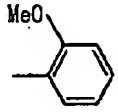
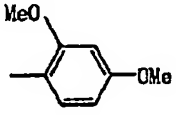
In the same way as in Example 1, each compound in accordance with Table 1 was produced.

(0075)

Table 1

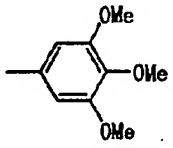
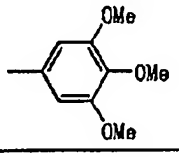
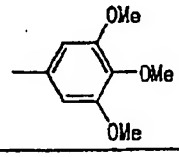
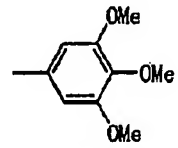
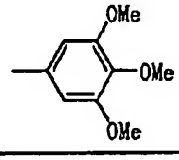
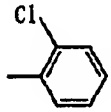
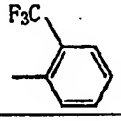


Me= material group, Et=ethyl group, n-Pr= n-propyl group, n-Bu= n-butyl group, n-Pe= n-pentyl group, n-Oct= n-octyl group, ph= phenyl group.

No.	R^1	R^2	X	Y	Z	mp. (°C) (Recrystallization solvent)
1	Ph		N	CH	C-CN	263～265
2	n-Bu		N	CH	C-CN	178～180 (Ethyl acetate-n-hexane)
3	n-Bu	Ph	CH	N	N	160～162 (Ethanol-n-hexane)
4	n-Bu		CH	N	N	150～151 (Ethanol-n-hexane)
5	n-Bu		CH	N	N	140～142 (Ethanol-n-hexane)
6	n-Bu		CH	N	N	200～202 (Ethanol-n-hexane)

(0076)

Table 1 (continued)

No.	R^1	R^2	X	Y	Z	mp. (°C) (Recrystallisation solvent)
7	Et		CH	N	N	179～181 (Ethanol-n-hexane)
8	n-Pr		CH	N	N	154～156 (Ethanol-n-hexane)
9	n-Bu		CH	N	N	148～150 (Ethanol-n-hexane)
10	n-Pe		CH	N	N	136～138 (Ethanol-n-hexane)
11	n-Oct		CH	N	N	101～103 (Ethanol-n-hexane)
12	n-Bu		CH	N	N	170～172 (Ethanol-n-hexane)
13	n-Bu		CH	N	N	124～126 (Ethyl acetate-n-hexane)

(0077)

Examples 14-39

The reaction same as in the said Reference Examples and Examples were carried out using suitable starting materials, and the following each compound were produced. Such compounds can be used as effective ingredients of this invention.

(0078)

Example 14

4-benzoylamino-2-n-butyl-8-cyano imidazo[1,5-a]pyrimidine.

(0079)

Example 15

2-n-butyl-8-cyano-4-(2-trifluoromethyl benzoylamino) imidazo[1,5-a]pyrimidine.

(0080)

(mp.: 192-195°C, recrystallization solvent: diethyl ether)

Example 16

2-n-butyl-8-cyano-4-(2-methylbenzoyl amino) imidazo[1,5-a]pyrimidine.

(0081)

Example 17

2-n-butyl-4-(2-chlorobenzoylamino)-8-cyano imidazo[1,5-a]pyrimidine.

(0082)

(mp.: 205-207°C, recrystallization solvent: ethanol-water).

Example 18

8-cyano-2-ethyl-4-(3,4,5-trimethoxy benzoylamino) imidazo[1,5-a]pyrimidine.

(0083)

Example 19

8-cyano-2-n-octyl-4-(3,4,5-trimethoxy benzoylamino) imidazo[1,5-a]pyrimidine.

(0084)

Example 20

2-n-butyl-4-(3,4,5-trimethoxy benzoylamino) imidazo[1,5-a]pyrimidine.

(0085)

Example 21

2-ethyl-4-(3,4,5-trimethoxy benzoylamino) imidazo[1,5-a]pyrimidine.

(0086)

Example 22

2-n-octyl-4-(3,4,5-trimethoxy benzoylamino) imidazo[1,5-a]pyrimidine.

(0087)

Example 23

2-n-butyl-4-(2-trifluoromethyl benzoylamino) imidazo[1,5-a]pyrimidine.

(0088)

Example 24

2-n-butyl-4-(2-methylbenzoyl amino) imidazo[1,5-a]pyrimidine.

(0089)

Example 25

2-n-butyl-4-(2-chlorobenzoylamino) imidazo[1,5-a]pyrimidine.

(0090)

Example 26

5-methyl-7-(3,4,5-trimethoxy benzoylamino)-1,2,4-triazolo[1,5-a]pyrimidine.

(0091)

Example 27

5-phenyl-7-(3,4,5-trimethoxy benzoylamino)-1,2,4-triazolo[1,5-a]pyrimidine.

(0092)

Example 28

7-benzoylamino-5-phenyl-1,2,4-triazolo[1,5-a]pyrimidine.

(0093)

Example 29

7-(2-methylbenzoyl amino)-5-phenyl-1,2,4-triazolo[1,5-a]pyrimidine.

(0094)

Example 30

7-(2-chlorobenzoylamino)-5-phenyl-1,2,4-triazolo[1,5-a]pyrimidine.

(0095)

Example 31

5-phenyl-7-(2-trifluoromethyl benzoylamino)-1,2,4-triazolo[1,5-a]pyrimidine.

(0096)

Example 32

5-n-butyl-7-(3,4,5-tri ethoxy benzoylamino)-1,2,4-triazolo[1,5-a]pyrimidine.

(0097)

Example 33

5-n-butyl-7-(2-pentafluoro ethyl benzoylamino)-1,2,4-triazolo[1,5-a]pyrimidine.

(0098)

Example 34

5-n-hexyl-7-(3,4,5-trimethoxy benzoylamino)-1,2,4-triazolo[1,5-a]pyrimidine.

(0099)

Example 35

5-n-heptyl-7-(3,4,5-trimethoxy benzoylamino)-1,2,4-triazolo[1,5-a]pyrimidine.

(0100)

Example 36

5-n-nonyl-7-(3,4,5-trimethoxy benzoylamino)-1,2,4-triazolo[1,5-a]pyrimidine.

(00101)

Example 37

5-n-decyl-7-(3,4,5-trimethoxy benzoylamino)-1,2,4-triazolo[1,5-a]pyrimidine.

(0102)

Example 38

5-n-butyl-7-(2,3,4-trimethoxy benzoylamino)-1,2,4-triazolo[1,5-a]pyrimidine.

(0103)

Example 39

5-n-butyl-7-(2,4,5-trimethoxy benzoylamino)-1,2,4-triazolo[1,5-a]pyrimidine.

(0104)

Examples 40 and 41

Production of 2-n-butyl-8-cyano-4-(2-methoxybenzoyl amino) imidazo[1,5-a]pyrimidine and 2-n-butyl-8-cyano-4-(N,N-bis [2-methoxybenzoyl] amino) imidazo[1,5-a]pyrimidine

Using the compound obtained in Reference Example 2 and 2-methoxybenzoyl chloride, the reaction same as in Example 1 was carried out, and crude product was recrystallised from

dichloromethane-diethyl ether, and colourless crystals of 2-n-butyl-8-cyano-4-(2-methoxybenzoyl amino) imidazo[1,5-a]pyrimidine were obtained. Thereafter the aforesaid recrystallization mother liquor was concentrated, and the residue was recrystallised from ethyl acetate, and colourless crystals of 2-n-butyl-8-cyano-4-(N,N-bis [2-methoxybenzoyl] amino) imidazo[1,5-a]pyrimidine were obtained. The structure and melting point of each obtained compound are shown in Table 2.

(0105)

Examples 42-54

In the same way as in Example 1, each compound in accordance with Table 2 was produced.

(0106)

Example 55

Production of 5-n-butyl-7-(2-methylsulfinyl benzoylamino)-1,2,4-triazolo[1,5-a]pyrimidine

30 % hydrogen peroxide water 0.4 g was added to acetic acid 20 ml solution of compound 1.0 g obtained in Example 54, and the mixture was stirred at room temperature for six hours. On completion of the reaction, water was added, and extraction was carried out with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, and was dried with anhydrous sodium sulphate, and concentration was carried out under reduced pressure. The residue was purified by silica gel column chromatography (eluate: chloroform : ethyl acetate = 1 : 2 to chloroform : methanol = 10 : 1), and furthermore it was recrystallised from ethanol-n-hexane, and colourless crystals 0.76 g of target compound were obtained. The structure and melting point of the obtained compound are shown in Table 2.

(0107)

Example 56

Production of 5-n-butyl-7-(2-methylsulfonyl benzoylamino)-1,2,4-triazolo[1,5-a]pyrimidine

30 % hydrogen peroxide water 0.8 g was added to acetic acid 20 ml solution of compound 1.0 g obtained in Example 54, and the mixture was stirred at 80°C for two hours. On completion of the reaction, water was added, and extraction was carried out with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried with anhydrous sodium sulphate, and concentration was carried out under reduced pressure. The residue was purified by silica gel column chromatography (eluate; chloroform : ethyl acetate = 1 : 2 to chloroform : methanol = 10 : 1) and further it was recrystallised from ethanol-n-hexane, and colourless crystals 0.67 g of target compound was obtained. The structure and melting point of the obtained compound are shown in Table 2.

(0108)

Example 57

In the same way as in Example 1, compound in accordance with Table 2 was produced.

(0109)

Example 58

In the same way as in Example 56, compound in accordance with Table 2 was produced.

(0110)

Examples 59-74

In the same way as in Example 1, each compound in accordance with Table 2 was produced.

(0111)

Example 75

In the same way as in Example 55, compound in accordance with Table 2 was produced.

(0112)

Example 76

In the same way as in Example 1, compound in accordance with Table 2 was produced.

(0113)

Example 77

Production of 5-n-butyl-7-(4-hydroxybenzoyl amino)-1,2,4-triazolo[1,5-a]pyrimidine

The ethanol 20 ml suspension of compound 1.41 g obtained in Example 76 was cooled to 0°C, and thereto was added 2N sodium hydroxide aqueous solution 5 ml and the mixture was stirred at 0°C for one hour. On completion of the reaction, it was concentrated under reduced pressure and the residue was diluted with water and was washed with dichloromethane. was The aqueous layer was made acidic by adding hydrochloric acid, and precipitated crude crystals were recovered by filtration, and recrystallised from ethanol-chloroform-n-hexane, and colourless crystals 1.12 g of target compound were obtained. The structure and melting point of the obtained compound are shown in Table 2.

(0114)

Example 78

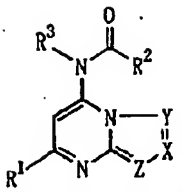
Production of 5-n-butyl-7-(N-n-butyl-N-[3,4,5-trimethoxy benzoyl] amino)-1,2,4-triazolo[1,5-a] pyrimidine

Compound 3.16 g obtained in Step (2) of Reference Example 11, n-butyl amine 1.10 g and sodium bicarbonate anhydride 1.26 g were added to ethanol 20 ml, and the mixture was stirred at 100°C for two hours. On completion of the reaction, it was concentrated under reduced pressure,

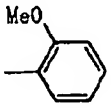
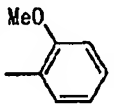
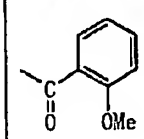
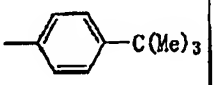
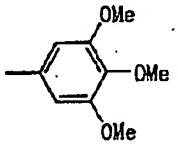
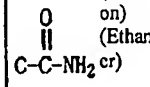
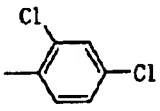
and water was added to the residue and extraction was carried out with ethyl acetate. The organic layer was recovered, dried with anhydrous sodium sulphate, and concentration was carried out under reduced pressure, and the crude product was obtained. This was purified by silica gel column chromatography (eluate; chloroform : ethyl acetate = 1 : 2) and further it was recrystallised from n-hexane, and 5-n-butyl-7-n-butylamino-1,2,4-triazolo[1,5-a]pyrimidine 2.72 g was obtained. Thereafter, using the obtained compound 1.12 g and 3,4,5-trimethoxy benzoyl chloride 1.08 g, colourless crystals 0.52 g of target compound was obtained in the same way as in Example 1. The structure and melting point of the obtained compound are shown in Table 2.

(0115)

Table 2

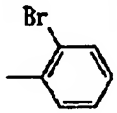
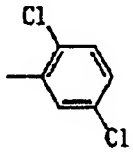
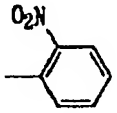
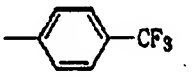
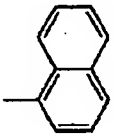
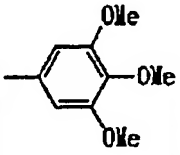


Me= material group, Et=ethyl group, n-Bu= n-butyl group, Ph= phenyl group, Ac= acetyl group.

No.	R^1	R^2	R^3	X	Y	Z	mp. (°C) (Recrystallisation solvent)
40	n-Bu		H	N	CH	C-CN	220～222 (Dichloromethane-diethyl ether)
41	n-Bu			N	CH	C-CN	183～185 (Ethyl acetate)
42	n-Bu		H	N	CH	C-CN	174～176 (Ethyl acetate-n-hexane)
43	n-Bu		H	N	CH		210 or more (Decomposition) (Ethanol water)
44	n-Bu		H	N	CH	C-CN	157～159 (Ethyl acetate-n-hexane)

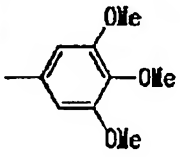
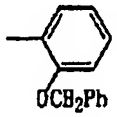
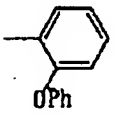
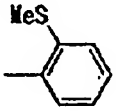
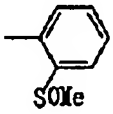
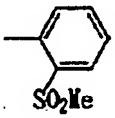
(0116)

Table 2 (continued)

No.	R^1	R^2	R^3	X	Y	Z	mp. (°C) (Recrystallisation solvent)
45	n-Bu		H	N	CH	C-CN	204~206 (Ethyl acetate-n-hexane)
46	n-Bu		H	N	CH	C-CN	194~196 (Ethyl acetate-n-hexane)
47	n-Bu		H	N	CH	C-CN	207~209 (Ethyl acetate diisopropyl ether)
48	n-Bu		H	N	CH	C-CN	203~205 (Ethanol water)
49	n-Bu		H	N	CH	C-CN	185~187 (Ethyl acetate)
50	Et		H	C-Ph	N	N	216~218 (Dichloromethane-n-hexane)

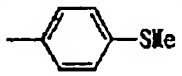
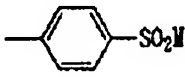
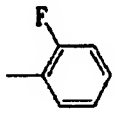
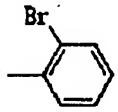
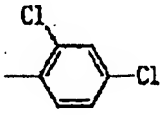
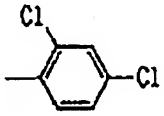
(0117)

Table 2 (continued)

No.	R^1	R^2	R^3	X	Y	Z	mp. (°C) (Recrystallisation solvent)
51	n-Bu		H	C-Ph	N	N	187~189 (Dichloromethane-n-hexane)
52	n-Bu		H	CH	N	N	170~172 (Ethanol-n-hexane)
53	n-Bu		H	CH	N	N	163~165 (Ethanol-n-hexane)
54	n-Bu		H	CH	N	N	128~130 (Ethanol-n-hexane)
55	n-Bu		H	CH	N	N	194~196 (Ethanol-n-hexane)
56	n-Bu		H	CH	N	N	211~213 (Ethanol-n-hexane)

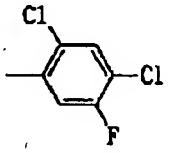
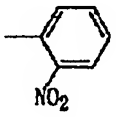
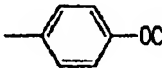
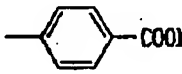
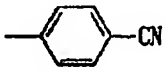
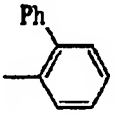
(0118)

Table 2 (continued)

No.	R^1	R^2	R^3	X	Y	Z	mp. (°C) (Recrystallisation solvent)
57	n-Bu		H	CH	N	N	144~146 (Ethanol-n-hexane)
58	n-Bu		H	CH	N	N	162~164 (Ethanol-n-hexane)
59	n-Bu		H	CH	N	N	203~206 (Ethanol-n-hexane)
60	n-Bu		H	CH	N	N	141~143 (Ethanol-n-hexane)
61	n-Bu		H	CH	N	N	106~108 (Ethanol-n-hexane)
62	n-Bu		H	C-Ph	N	N	207~209 (Ethanol-n-hexane)

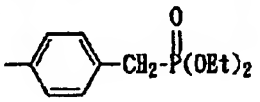
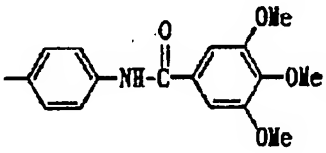
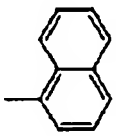
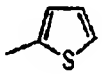
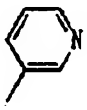
(0119)

Table 2 (continued)

No.	R^1	R^2	R^3	X	Y	Z	mp. (°C) (Recrystallisation solvent)
63	n-Bu		H	CH	N	N	171~173 (Ethanol-n-hexane)
64	n-Bu		H	CH	N	N	136~138 (Ethanol-n-hexane)
65	n-Bu		H	CH	N	N	143~145 (Ethyl acetate-n-hexane)
66	n-Bu		H	CH	N	N	124~126 (Ethanol-n-hexane)
67	n-Bu		H	CH	N	N	169~171 (Ethanol-n-hexane)
68	n-Bu		H	CH	N	N	Oily substance ^{1}H-NMR (1)

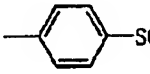
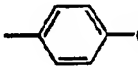
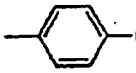
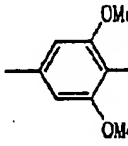
(0120)

Table 2 (continued)

No.	R^1	R^2	R^3	X	Y	Z	mp. (°C) (Recrystallisation solvent)
69	n-Bu		H	CH	N	N	Oily substance ^{1}H-NMR (2)
70	n-Bu		H	CH	N	N	202~205 (Chloroform-n-hexane)
71	n-Bu		H	CH	N	N	98~100 (Ethanol-n-hexane)
72	n-Bu		H	CH	N	N	166~168 (Ethanol-n-hexane)
73	n-Bu		H	CH	N	N	157~159 (Ethanol-n-hexane)
74	n-Bu		H	CH	N	N	141~143 (Ethanol-n-hexane)

(0121)

Table 2 (continued)

No.	R^1	R^2	R^3	X	Y	Z	mp. (°C) (Recrystallisation solvent)
75	n-Bu		H	CH	N	N	115～118 (Ethanol-n-hexane)
76	n-Bu		H	CH	N	N	105～107 (Ethanol-n-hexane)
77	n-Bu		H	CH	N	N	260～262 (Ethanol-chloroform-n-hexane)
78	n-Bu		n-Bu	CH	N	N	102～104 (Ethanol-n-hexane)

(0122)

Table 2 (continued)

No.	1H-NMR (δ : ppm)
68	0.96 (3H, t, J=7.3), 1.3～1.5 (2H, m), 1.7～1.9 (2H, m), 2.89 (2H, t, J=7.8), 7.2～7.7 (8H, m), 7.82 (1H, s), 7.90 (1H, m), 8.14 (1H, s), 8.77 (1H, brs) [CDCl3]
69	0.97 (3H, t, J=7.3), 1.28 (6H, t, J=7.1), 1.4～1.5 (2H, m), 1.8～1.9 (2H, m), 2.96 (2H, t, J=7.8), 3.27 (2H, d, J=22), 4.0～4.1 (4H, m), 7.54 (2H, dd, J=8.4, 2.5), 7.9～8.0 (3H, m), 8.41 (1H, s), 9.68 (1H, brs) [CDCl3]

(0123)

Examples 79-141

The following each compound can be produced by carrying out the reaction same as in Reference Examples and Examples using suitable starting materials. All these compounds can be used as effective ingredients in this invention.

(0124)

Example 79

7-(4-benzyloxy benzoylamino)-5-n-butyl-2-phenyl-1,2,4-triazolo[1,5-a]pyrimidine.

(0125)

Example 80

7-(2-benzyloxy benzoylamino)-5-n-butyl-2-phenyl-1,2,4-triazolo[1,5-a]pyrimidine.

(0126)

Example 81

5-n-butyl-7-(2-phenoxy benzoylamino)-2-phenyl-1,2,4-triazolo[1,5-a]pyrimidine.

(0127)

Example 82

5-n-butyl-7-(2-methylthio benzoylamino)-2-phenyl-1,2,4-triazolo[1,5-a]pyrimidine.

(0128)

Example 83

5-n-butyl-7-(2-methylsulfinyl benzoylamino)-2-phenyl-1,2,4-triazolo[1,5-a]pyrimidine.

(0129)

Example 84

5-n-butyl-7-(2-methylsulfonyl benzoylamino)-2-phenyl-1,2,4-triazolo[1,5-a]pyrimidine.

(0130)

Example 85

5-n-butyl-7-(2-chlorobenzoylamino)-2-phenyl-1,2,4-triazolo[1,5-a]pyrimidine.

(0131)

Example 86

5-n-butyl-7-(2,4-dichloro-5-fluorobenzoyl amino)-2-phenyl-1,2,4-triazolo[1,5-a]pyrimidine.

(0132)

Example 87

5-n-butyl-7-(2-nitrobenzoyl amino)-2-phenyl-1,2,4-triazolo[1,5-a]pyrimidine.

(0133)

Example 88

5-n-butyl-2-phenyl-7-(2-trifluoromethyl benzoylamino)-1,2,4-triazolo[1,5-a]pyrimidine.

(0134)

Example 89

5-n-butyl-2-phenyl-7-(4-trifluoromethoxybenzoyl amino)-1,2,4-triazolo[1,5-a]pyrimidine.

(0135)

Example 90

5-n-butyl-7-(4-methoxycarbonyl benzoylamino)-2-phenyl-1,2,4-triazolo[1,5-a]pyrimidine.

(0136)

Example 91

5-n-butyl-7-(4-cyano benzoylamino)-2-phenyl-1,2,4-triazolo[1,5-a]pyrimidine.

(0137)

Example 92

5-n-butyl-2-phenyl-7-(2-phenylbenzo ylamino)-1,2,4-triazolo[1,5-a]pyrimidine.

(0138)

Example 93

5-n-butyl-7-(4-diethoxy phosphoryl methylbenzoyl amino)-2-phenyl-1,2,4-triazolo[1,5-a] pyrimidine.

(0139)

Example 94

5-n-butyl-2-phenyl-7-(4-(3,4,5-trimethoxy benzoylamino) benzoylamino)-1,2,4-triazolo[1,5-a] pyrimidine.

(0140)

Example 95

5-n-butyl-7-(1-naphthoyl amino)-2-phenyl-1,2,4-triazolo[1,5-a]pyrimidine.

(0141)

Example 96

5-n-butyl-7-(2-furoyl amino)-2-phenyl-1,2,4-triazolo[1,5-a]pyrimidine.

(0142)

Example 97

5-n-butyl-2-phenyl-7-(2-thenoyl amino)-1,2,4-triazolo[1,5-a]pyrimidine.

(0143)

Example 98

5-n-butyl-7-(isonicotinoyl amino)-2-phenyl-1,2,4-triazolo[1,5-a]pyrimidine.

(0144)

Example 99

7-(2-acetoxy benzoylamino)-5-n-butyl-2-phenyl-1,2,4-triazolo[1,5-a]pyrimidine.

(0145)

Example 100

5-n-butyl-7-(2-hydroxybenzoyl amino)-2-phenyl-1,2,4-triazolo[1,5-a]pyrimidine.

(0146)

Example 101

2-n-butyl-4-(benzyloxy benzoylamino)-8-cyano imidazo[1,5-a]pyrimidine.

(0147)

Example 102

2-n-butyl-8-cyano-4-(2-phenoxy benzoylamino) imidazo[1,5-a]pyrimidine.

(0148)

Example 103

2-n-butyl-8-cyano-4-(2-methylthio benzoylamino) imidazo[1,5-a]pyrimidine.

(0149)

Example 104

2-n-butyl-8-cyano-4-(2-methylsulfinyl benzoylamino) imidazo[1,5-a]pyrimidine.

(0150)

Example 105

2-n-butyl-8-cyano-4-(2-methylsulfonyl benzoylamino) imidazo[1,5-a]pyrimidine.

(0151)

Example 106

2-n-butyl-8-cyano-4-(4-trifluoromethoxybenzoyl amino) imidazo[1,5-a]pyrimidine.

(0152)

Example 107

2-n-butyl-8-cyano-4-(4-methoxycarbonyl benzoylamino) imidazo[1,5-a]pyrimidine.

(0153)

Example 108

2-n-butyl-8-cyano-4-(4-cyano benzoylamino) imidazo[1,5-a]pyrimidine.

(0154)

Example 109

2-n-butyl-8-cyano-4-(2-phenyl benzoylamino) imidazo[1,5-a]pyrimidine.

(0155)

Example 110

2-n-butyl-8-cyano-4-(4-diethoxy phosphoryl methylbenzoyl amino) imidazo[1,5-a]pyrimidine.

(0156)

Example 111

2-n-butyl-8-cyano-4-(4-(3,4,5-trimethoxy benzoylamino) benzoylamino) imidazo[1,5-a] pyrimidine.

(0157)

Example 112

2-n-butyl-8-cyano-4-(2-furoyl amino) imidazo[1,5-a]pyrimidine.

(0158)

Example 113

2-n-butyl-8-cyano-4-(2-thenoyl amino) imidazo[1,5-a]pyrimidine.

(0159)

Example 114

2-n-butyl-8-cyano-4-(isonicotinoyl amino) imidazo[1,5-a]pyrimidine.

(0160)

Example 115

4-(2-acetoxy benzoylamino)-2-n-butyl-8-cyano imidazo[1,5-a]pyrimidine.

(0161)

Example 116

2-n-butyl-8-cyano-4-(2-hydroxybenzoyl amino) imidazo[1,5-a]pyrimidine.

(0162)

Example 117

2-n-butyl-4-(2-benzyloxy benzoylamino)-8-carbamoyl imidazo[1,5-a]pyrimidine.

(0163)

Example 118

2-n-butyl-8-carbamoyl-4-(2-phenoxy benzoylamino) imidazo[1,5-a]pyrimidine.

(0164)

Example 119

2-n-butyl-8-carbamoyl-4-(2-chlorobenzoylamino) imidazo[1,5-a]pyrimidine.

(0165)

Example 120

2-n-butyl-8-carbamoyl-4-(2,4-dichlorobenzoyl amino) imidazo[1,5-a]pyrimidine.

(0166)

Example 121

2-n-butyl-8-carbamoyl-4-(2-nitrobenzoyl amino) imidazo[1,5-a]pyrimidine.

(0167)

Example 122

2-n-butyl-8-carbamoyl-4-(2-trifluoromethyl benzoylamino)-imidazo[1,5-a]pyrimidine.

(0168)

Example 123

2-n-butyl-8-carbamoyl-4-(2-methylthio benzoylamino) imidazo[1,5-a]pyrimidine.

(0169)

Example 124

2-n-butyl-8-carbamoyl-4-(2-methylsulfinyl benzoylamino) imidazo[1,5-a]pyrimidine.

(0170)

Example 125

2-n-butyl-8-carbamoyl-4-(2-methylsulfonyl benzoylamino) imidazo[1,5-a]pyrimidine.

(0171)

Example 126

2-n-butyl-8-carbamoyl-4-(4-trifluoromethoxybenzoyl amino) imidazo[1,5-a]pyrimidine.

(0172)

Example 127

2-n-butyl-8-carbamoyl-4-(4-methoxycarbonyl benzoylamino) imidazo[1,5-a]pyrimidine.

(0173)

Example 128

2-n-butyl-8-carbamoyl-4-(4-cyano benzoylamino) imidazo[1,5-a]pyrimidine.

(0174)

Example 129

2-n-butyl-8-carbamoyl-4-(2-phenyl benzoylamino) imidazo[1,5-a]pyrimidine.

(0175)

Example 130

2-n-butyl-8-carbamoyl-4-(4-diethoxy phosphoryl methylbenzoyl amino) imidazo[1,5-a] pyrimidine.

(0176)

Example 131

2-n-butyl-8-carbamoyl-4-(4-(3,4,5-trimethoxy benzoylamino) benzoylamino) imidazo[1,5-a] pyrimidine.

(0177)

Example 132

2-n-butyl-8-carbamoyl-4-(1-naphthoyl amino) imidazo[1,5-a]pyrimidine.

(0178)

Example 133

2-n-butyl-8-carbamoyl-4-(2-furoyl amino) imidazo[1,5-a]pyrimidine.

(0179)

Example 134

2-n-butyl-8-carbamoyl-4-(2-thenoyl amino) imidazo[1,5-a]pyrimidine.

(0180)

Example 135

2-n-butyl-8-carbamoyl-4-(isonicotinoyl amino) imidazo[1,5-a]pyrimidine.

(0181)

Example 136

4-(2-acetoxy benzoylamino)-2-n-butyl-8-carbamoyl imidazo[1,5-a]pyrimidine.

(0182)

Example 137

2-n-butyl-8-carbamoyl-4-(2-hydroxybenzoyl amino) imidazo[1,5-a]pyrimidine.

(0183)

Example 138

2-n-butyl-8-carbamoyl-4-(2-methoxybenzoyl amino) imidazo[1,5-a]pyrimidine.

(0184)

Example 139

2-n-butyl-4-(4-t-butylbenzo ylamino)-8-carbamoyl imidazo[1,5-a]pyrimidine.

(0185)

Example 140

2-n-butyl-8-carbamoyl-4-(2-bromobenzoyl amino) imidazo[1,5-a]pyrimidine.

(0186)

Example 141

2-n-butyl-8-carbamoyl-4-(N,N-bis [2-methoxybenzoyl] amino) imidazo[1,5-a]pyrimidine.

(0187)

Pharmacological Test Example 1

Using seven 6-week old S.D. male rats per group, firstly pain threshold of left hind leg footpad of each rat was measured in accordance with Randall • Sellitto method (Randall, L.O. and Sellitto, J.J, Arch. Int. Pharmacodyn., 111, 409 (1957)) using pressure stimulation analgesia effect

measuring apparatus (made by Unicom Co.). The obtained value was used as the "previous value".

(0188)

After 1 hour of the aforesaid measurement of previous value, oral administration was carried out with 5 % gum arabic suspension of effective ingredient compound of this invention to the test groups and with 5 % gum arabic suspension (not including effective ingredient compound of this invention) to the control group in proportion of 10 ml/kg (effective component dose of 1 mg/kg) respectively, and further one hour later, physiological saline solution (25 ng/0.1 ml) of substance P was subcutaneously injected into left hind leg footpad of each rat.

(0189)

Next, after prescribed time from the substance P injection, the pain threshold of the left hind leg footpad of the rat of each group was measured in the same way as described above, and it was used as "post-treatment value".

(0190)

From the measured value (post-treatment value) and the previous value of each group, pain threshold recovery rate (%) was calculated according to the following equation.

(0191)

Pain threshold recovery rate (%) = [(Test group average post-treatment value) - (Control group average post-treatment value)] / [(Control group average previous value) - (Test group average post-treatment value)] x 100

The obtained results (the maximum recovery rate) are shown in following Table 3.

(0192)

Table 3

Example No.	Recovery Rate (%)	Time of measurement (mins later)
2	41.6	30
4	41.9	60
7	37.5	60
9	58.9	60
12	33.5	30
15	34.5	15
44*	72.0	60
49*	45.5	30
57*	34.1	30

*: Dose = 10 mg/kg

(0193)

From the aforesaid Table 3, it is clear that the effective ingredient compounds of this invention have excellent analgesic action.

(0194)

Pharmacological Test Example 2

Spraque Dawley male rats (6-9 weeks old, 200-250 g) were slaughtered by cervical spine dislocation, and thoracic aorta was extracted promptly, and surrounding connective tissues were peeled off. Next, the aorta was cut into 5-7 rings, each was sliced open longitudinally, and thereafter intravascular cavity was abraded using a washed swab thereby eliminating endothelial cells in order to eliminate the effect of cNOS present in vascular endothelial cells, and sample was prepared.

(0195)

The aforesaid sample was introduced into Krebs-Henseleit liquid (NaCl 118.3 mM, KCl 4.7 mM, CaCl2 2.5 mM, KH2PO4 1.2 mM, $MgSO_4$ 1.2 mM, NaHCO3 25.0 mM and glucose 11.1 mM) wherein dimethylsulfoxide solution of effective ingredient compound of this invention (test compound) which was prepared in 30 μM concentration was added and L-arginine was further added so as to become 400 μM concentration, and the mixture was incubated at 37°C for 30 minutes. Continuing lipopolysaccharide (LPS) was added by 1000 ng/ml concentration, and it was incubated at 37°C for 24 hours (experimental group using test compound, group of this invention).

(0196)

Next, supernatant was sampled on 96-well plate, and NO2 was coloured with Griess liquid according to NO2 measurement method described in literature (New Biochemistry Experiment chair 10, blood vessel, endothelium and smooth muscle, 135 pages, Jpn Biochem Soc Eds, Tokyo Kagaku Dojin, 1993) and it was measured using Biokinetics Reader (EL-340 model, made by BIO-TEK Instruments company), and accumulated NO2 amount was calculated.

(0197)

Moreover, the sample of blood vessel piece was dissolved in 1N sodium hydroxide aqueous solution, and it was coloured with Bio-Rad DC protein assay kit (made by Bio-Rad Laboratories Co) and it was measured with spectrophotometer (made by HITACHI Co, U-3000 model), and protein content was calculated. Moreover, from these values, the quantity of NO2 formed per protein 1 mg was determined.

(0198)

On the other hand, the same test was carried out for the control group with the addition of dimethylsulfoxide instead of the test compound for the negative control group without even the addition of LPS.

(0199)

The iNOS induction inhibition rate was determined according to the following equation from NO2 quantity formed per protein 1 mg in each group obtained as above.

(0200)

Inhibition rate (%) ={1- [(this invention group value) - (negative control group value)] / [control group value) - (negative control group value)]} x 100

The obtained results are shown in the Table 4.

(0201)

Table 4

Example No.	Inhibitory rate (%)
2	80.2
44	102.9

(0202)

From Table 4, it is clear that the effective ingredient compounds of this invention inhibited the induction of iNOS by LPS.

(0203)

Preparation Example 1.

Preparation of tablets.

Using compound obtained in Example 9 as effective ingredient of tablet, tablet for oral administration containing 5 mg per tablet (1000 tablets) were prepared by the following formulation.

(0204)

Compound obtained in Example 9	5 g
lactose (Pharmacopeia of Japan product)	50 g
corn starch (Pharmacopeia of Japan product)	25 g
crystalline cellulose (Pharmacopeia of Japan product)	25 g
methyl cellulose (Pharmacopeia of Japan product)	1.5 g
magnesium stearate (Pharmacopeia of Japan product)	1 g

Namely, the compound obtained in Example 9, lactose, corn starch and crystalline cellulose were mixed thoroughly according to the aforesaid formulation, and the mixture was granulated using methyl cellulose 5 % aqueous solution and was passed through sieve of 200 mesh and it was carefully dried, thereafter, it was passed through sieve of 200 mesh, this was mixed with magnesium stearate, and the mixture was pressed into tablets, and desired tablets were obtained.

(0205)

Preparation Example 2.

Preparation of capsule agent.

Two-piece hard gelatin capsule (1000 capsules) for oral administration containing 10 mg per capsule was prepared by following formulation using compound obtained in Example 44 as effective ingredient of encapsulated formulation.

(0206)

Compound obtained in Example 44	10 g
lactose (Pharmacopeia of Japan product)	80 g
starch (Pharmacopeia of Japan product)	30 g
talc (Pharmacopeia of Japan product)	5 g
magnesium stearate (Pharmacopeia of Japan product)	1 g

Namely, each component was made into fine powder according to the aforesaid formulation, and the mixture was thoroughly stirred to form a uniform mixture, and it was packed into capsule for the oral administration having desired dimension, and the target encapsulated formulation was obtained.

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